REMARKS

Status of the Claims

Claims 1-11, 19, 22, and 23 are pending in the present application. Claims 1, 22 and 23 have been amended to recite that the isolated nucleic acid sequences of the invention, as well as the plants and plant cell comprising the nucleic acid sequences of the invention, encompass nucleic acid sequences that have at least 90% nucleotide sequence identity to SEQ ID NO:1, 3, or 5, or encode a protein having at least 90% amino acid sequence identity to SEQ ID NO:2, 4, or 6. Support for this amendment can be found in the specification, for example, on page 9, lines 11-16. Claim 1 has been further amended to correct a typographical error. Claim 11 has been amended for purposes of clarification. Support for this amendment can be found, for example, on page 23, lines 19-29. No new matter has been added by way of this amendment.

The Examiner is respectfully requested to withdraw the rejection and allow claims 1-11, 19, 22, and 23. In any event, the Examiner is requested to enter the above amendments for purposes of furthering prosecution. These amendments were not made earlier because Applicant earnestly believes that the specification is enabling for the breadth of the claims as originally drafted. Reconsideration and reexamination is respectfully requested in view of the following remarks.

The Rejections Under 35 U.S.C. § 112, First Paragraph, Should be Withdrawn

Enablement

The Examiner rejected claims 1-11, 19 and 22-23 under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not enable one skilled in the art to make or use the invention. This rejection is respectfully traversed.

The Examiner asserts that the specification, while enabling for nucleic acids encoding SEQ ID NO:2, 4, or 6, host cells, plants, plant cells and seeds comprising them, and a method of using them to make SEQ ID NO:2, 4, or 6, does not reasonably provide enablement for methods and compositions drawn to nucleic acids encoding pesticidal proteins with 95% sequence identity to SEQ ID NO:2, 4, or 6, nucleic acids with 95% identity to SEQ ID NO:1, 3, or 5, or a complement of those nucleic acids, host cells, plants, plant cells and seeds comprising them, and

a method of using them to make a pesticidal protein with 95% identity to SEQ ID NO:1, 3, or 5. The Examiner states that the specification fails to provide guidance for which amino acids of SEQ ID NO:2, 4, or 6 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain the activity of the encoded protein, as well as which regions of the protein can tolerate insertions and still produce a functional protein. Claims 1, 22 and 23 have been amended to recite that the isolated nucleic acid sequences of the invention, as well as the plants and plant cell comprising the nucleic acid sequences of the invention, encompass nucleic acid sequences that have at least 90% nucleotide sequence identity to SEQ ID NO:1, 3, or 5, or encode a protein having at least 90% amino acid sequence identity to SEQ ID NO:2, 4, or 6.

The Examiner appears to be suggesting that, in order to satisfy the enablement requirement, Applicants must demonstrate that every pesticidal polypeptide and variant and fragment thereof encompassed by the claims could be used to successfully practice the invention, such that no experimentation would be required. According to the applicable case law, however, the test of enablement is not whether experimentation is necessary to make and use an invention, but rather if experimentation is necessary, whether it is undue. *In re Angstadt*, 198 USPQ 214, 219 (C.C.P.A. 1976). Furthermore, a considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The test of whether an invention requires undue experimentation is not based on a single factor, but rather is a conclusion reached by weighing many factors. *Id.* at 1404. Factors to be considered in determining whether undue experimentation is required include the quantity of experimentation necessary, the amount of guidance provided in the specification, the presence of working examples of the invention in the application, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability in the art, and the breadth of the claimed invention. *Id.* Accordingly, the holding of *Wands* does not require that Applicants provide as working examples every pesticidal polypeptide that could be used to practice the present invention. Rather, *Wands* sets out factors to be considered in determining whether undue experimentation is required to make and use the invention.

The Examiner maintains that the specification does not enable one of skill in the art to make and use nucleic acids that encode polypeptides that retain pesticidal activity and have at least 95% sequence identity to SEQ ID NO:1, 3, or 5, or 95% sequence identity to a nucleotide sequence that encodes SEQ ID NO:2, 4, or 6. The Examiner incorrectly bases this conclusion solely on the number of possible nucleic acids having the recited percent identity to SEQ ID NO:1, 3, or 5, or a nucleotide sequence encoding SEQ ID NO:2, 4, or 6 while continuing to dismiss the other factors set forth in *Wands* for assessing whether undue experimentation is required. In particular, the Examiner has continued to discount the guidance provided in the specification and the working examples set forth in the application (page 6 of the Office Action mailed August 15, 2006).

First, sufficient guidance for making and using the recited sequences is present in the specification. The claimed variants and fragments of SEQ ID NO:1, 3, or 5, or nucleotide sequences encoding SEQ ID NO:2, 4, or 6 are limited by a percent identity (i.e., 90% identity) and further limited by the functional requirement that they possess pesticidal activity. Guidance for preparing variants and fragments of SEQ ID NO:1, 3, or 5, or nucleotide sequences encoding SEQ ID NO:2, 4, or 6 and for determining percent identity is provided in the specification and generally known in the art. See pages 9-13. Numerous delta-endotoxins were also well known in the art at the time the application was filed. See Crickmore *et al.* (1998) *Microbiol. Molec. Biol. Rev.* 62:807-813, which is incorporated by reference on page 2, lines 7-8 and was submitted with the response filed on June 2, 2006. The necessary molecular biology and mutagenesis techniques for preparing the variants and fragments of pesticidal sequences of the invention are routine. Moreover, methods for assessing the pesticidal activity of a polypeptide are readily available in the art and provided in the specification. See, for example, page 11, lines 15-19 and Examples 7 and 9-12.

In order to identify the pesticidal sequences encompassed by the present claims, one of skill in the art would only need to prepare variants and fragments of the nucleotide sequence of SEQ ID NO:1, 3, or 5, or a nucleotide sequence encoding SEQ ID NO:2, 4, or 6, having the specified characteristics recited in the claims (e.g., at least 90% identity) and then assay these polypeptides for pesticidal activity. Routine methods for preparing variants and fragments and

testing the resulting polypeptides for pesticidal activity are routine in the art and described in the specification. Although some experimentation is required to practice the claimed invention, it is now customary in the art to generate a large number of sequences and to test them in a large-scale assay for a desired function, and, therefore, such experimentation is not undue, particularly in view of the routine nature of the required methods. Contrary to the Examiner's conclusions, in order to identify variants and fragments of the nucleotide sequence of SEQ ID NO:1, 3, or 5, or a nucleotide sequence encoding SEQ ID NO:2, 4, or 6 that could be used in the invention, a person skilled in the art would only need to utilize standard molecular biology and mutagenesis techniques and routine screening tests for pesticidal activity. Therefore, given the level of skill and knowledge in the art, the availability of standard methods and assays, and the significant guidance provided in the specification, Applicants respectfully submit that the amount of experimentation required to identify delta-endotoxins and variants and fragments thereof having pesticidal activity and the structural features recited in the claims is routine, not undue.

In support of the argument that the invention is not enabled throughout the full scope of the claims, the Examiner cites *Genentech, Inc. v. Novo Nordisk, A/S*, 42 USPQ 2d 1001, 1005 (Fed. Cir. 1997) which, according to the Examiner, teaches that disclosure of a "mere germ of an idea does not constitute [an] enabling disclosure", and that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention (page 7 of the August 15, 2006 Office Action). Upon full review of this opinion, the Applicants contend that the *Genentech* decision actually supports the assertion that the invention is fully enabled.

The question before the Court in *Genentech* was whether the specification of U.S. Patent 5,424,199 would have enabled a skilled artisan to use cleavable fusion expression to make hGH without undue experimentation. The Court concluded that the specification does not describe in any detail whatsoever how to make hGH using cleavable fusion expression, and that no description of any specific cleavable conjugate protein appears. Contrarily, in the instant specification, specific nucleotide sequences encoding proteins with pesticidal activity, as well as fragments thereof, are provided (SEQ ID NO:1, 3, and 5), and sufficient guidance for preparing variants and fragments of SEQ ID NO:1, 3, or 5, or nucleotide sequences encoding SEQ ID NO:2, 4, or 6, and for determining percent identity is provided in the specification.

Further, although the Court does state that the "mere germ of an idea does not constitute an enabling disclosure", it immediately follows with the opinion that "[w]hile every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." In citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986), the Court reiterates that "a specification need not disclose what is well known in the art" and characterizes "undue experimentation" as that in which "there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out".

As noted above, the instant specification clearly provides starting material (SEQ ID NO:1-6) as well as extensive description regarding the conditions under which amino acid substitutions can be carried out to generate a nucleotide sequence with at least 90% sequence identity to SEQ ID NO:1, 3, or 5, or a nucleotide sequence that encodes an amino acid sequence that is at least 90% identical to SEQ ID NO:2, 4, or 6. For instance, the specification describes examples of conserved residues that are not likely to tolerate substitution (see page 13), delineates conserved domains characteristic of delta-endotoxin proteins (see page 4), and highlights conserved residues in the sequences of the invention (see Figure 1 as originally filed). Further, routine methods for preparing variants and fragments and testing the resulting polypeptides for pesticidal activity are described in the specification.

The Examiner also cites *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at 1027 in support of rejection of the claims for lack of enablement. Similar to the *Genentech* decision, the opinion provided by the Court in *Amgen* further supports the enablement of the present invention. As noted by the Examiner, the Court acknowledges that the disclosure in the Amgen patent (which provides a few EPO analog genes) "might well justify a generic claim encompassing these [EPO analog genes] and similar analogs". The Court ruled that the disclosure was inadequate support for Amgen's desire to claim *all* EPO gene analogs. There is no such claim in the instant application. Rather, the claims encompass specific nucleotide sequences (SEQ ID NO:1, 3, and 5), as well as nucleotide sequences with at least 90% sequence identity to SEQ ID NO:1, 3, or 5, or nucleotide sequences that encode an amino acid sequence

that is at least 90% identical to SEQ ID NO:2, 4, or 6 (i.e., "similar analogs"). Therefore, the Applicants contend that the claims at issue in the *Amgen* decision are not related to the claims of the instant application, and that the opinion expressed by the Court in this decision actually *supports* the Applicants assertion that the claims are fully enabled.

The Examiner also maintains that mutation of sequences, even conservative substitutions, does not produce predictable results and, therefore, the specification is not enabling with respect to variants of the nucleotide sequence of SEQ ID NO:1, 3, or 5, or a nucleotide sequence encoding SEQ ID NO:2, 4, or 6. The Examiner continues to rely on Lazar *et al.* (1988) *Molecular and Cellular Biology* 8:1247-1252 and Hill *et al.* (1998) *Biochem. Biophys. Res. Comm.* 244:573-577 in support of the general unpredictability of the art with respect to modification of nucleotide sequences. The Examiner asserts that the unpredictability is predicated on the fact that a "conservative" substitution reduced biological function of transforming growth factor alpha while "nonconservative" substitutions had no effect. However, regardless of the nature of the substitution (conservative vs. nonconservative), the alteration in the polypeptide was specifically designed to occur at amino acid positions that are highly conserved in the EGF-like family of polypeptides. Similarly, the modified residues described by Hill *et al.* were conserved among bacterial and plant ADP-glucose pyrophosphorylases. As noted previously, the first line of the abstract, "[t]wo *absolutely conserved* histidines and a third *highly conserved* histidine are noted in eleven bacterial and plant ADP-glucose pyrophosphorylases" (emphasis added). Again, one of skill in the art would not be surprised that modification of one of these highly conserved amino acids would lead to the loss of function described by the authors.

The Examiner stated that the surprise in Lazar *et al.* and Hill *et al.* was that these highly conserved amino acids in these well-characterized proteins did not behave as expected, and suggested that "the conventional wisdom about using conserved amino acids to guide the making of amino acid substitutions is wrong" (page 8 of the August 15, 2006 Office Action). The Applicants respectfully disagree with this unsubstantiated assertion by the Examiner. Conventional wisdom may, in fact, hinge on the vast preponderance of evidence that supports the

Applicants position that the majority of conservative substitutions made in nonconserved regions have little or no effect on protein function.

For example, Jenkins *et al.* (1999) *FEBS Letters* 462:373-376 and Rajamohan *et al.* (1996) *J Biol. Chem.* 271(41):25220-25226 (provided in Appendices B and C, respectively, of the amendment filed October 16, 2006), both demonstrate that non-conservative substitutions in non-conserved regions of delta-endotoxin proteins result in a loss of activity. While Rajamohan *et al.* do show that a conservative substitution in a non-conserved region can lead to a decrease (though not elimination) of activity, the non-conservative substitutions in these same regions have a much more significant impact on protein function.

Similarly, Lee *et al.* (2001) *FEBS Letters* 497:108-112 (provided in appendix D of the amendment filed October 16, 2006) show that several conservative substitutions in a non-conserved region (F276A and F280A) of Cry1Ac had no effect on toxicity, while many non-conservative substitutions in this non-conserved region of the protein eliminated toxicity of Cry1Ac toward *Manduca sexta* and *Lymantria dispar.* Schwartz *et al.* (1997) *Appl. Environ. Microbiol.* 63(10): 3978-3984 and Masson *et al.* (2002) *Appl. Environ. Microbiol.* 68(1):194-200 (provided in Appendices E and F, respectively, of the amendment filed October 16, 2006) show that both conservative and non-conservative substitutions in the conserved group 4 residues result in a decrease in toxicity of Cry1Aa and Cry1Ac proteins toward dipteran and lepidopteran pests, respectively.

Furthermore, the specification provides guidance regarding conservative modifications in *nonconserved* regions that are unlikely to disrupt biological activity (rather than conserved regions as is taught by both Lazar *et al.* and Hill *et al.*). See, for example, pages 12-14. Thus, by reference to a standard codon table, one of skill in the art could predict which modifications would not affect the biological activity of the encoded polypeptide. Also, the specification describes examples of conserved residues that are not likely to tolerate substitution (see page 13-14), delineates conserved domains characteristic of delta-endotoxin proteins (see page 4), and highlights conserved residues in the sequences of the invention (see Figure 1 as originally filed). One of skill in the art would understand that, in order to preserve function, amino acid substitutions of any nature should not be made in conserved regions of a protein. Therefore, the

Examiner has failed to explain the relevance of Lazar *et al.* and Hill *et al.* to the present application since these two experiments targeted conserved regions of each protein under investigation.

The Examiner also urges that making amino acid substitutions in SEQ ID NO:2, 4, or 6 would need to be done randomly, that random substitutions have a likelihood of failure, and that the likelihood of failure amounts to undue experimentation. The Examiner relies on the teachings of Guo *et al.* (2004) *Proc. Natl. Acad. Sci. USA* 101:9205-9210 for the proposition that increasing the number of amino acid substitutions in a protein increases the probability that the protein will be functionally inactivated (i.e., "likelihood of failure"). As an initial matter, if one in fact wishes to make all 102 possible amino acid substitutions (as the Examiner contends is necessary to practice the full scope of the invention), the experimentation would be the same, regardless of the likelihood of failure. Even Guo *et al.* suggest that the inactivation probability is only around 34%, which hardly constitutes a "likelihood of failure." Guo *et al.* further disclose that the 34% probability is based on data from a simple monomeric protein (which delta-endotoxins are not), and contends that the isolation of active mutants harboring many mutations from large random mutagenesis libraries is not surprising (page 9209, column 2 of Guo *et al.*).

Secondly, as discussed extensively herein, the specification provides sufficient guidance with respect to which amino acids are not likely to tolerate substitutions such that the making of amino acids with at least 90% sequence identity to SEQ ID NO:2, 4, or 6 *does not* require "random" substitution.

Further, detailed information about the structure of delta-endotoxins was also known in the art. See, for example, Li *et al.* (1991) *Nature* 353:815-821 (describing the crystal structure of the Cry3A protein), which is incorporated by reference on page 13 of the specification, and Morse *et al.* (2001) *Structure* 9:409-417, both of which were submitted with the June 2, 2006 response. Delta-endotoxins are extremely well-characterized and related to each other to various degrees by similarities in their amino acid sequences and tertiary structures. A combined consideration of the published structural analyses of delta-endotoxins and the reported functions associated with particular structures, motifs, and the like indicates that specific regions of the toxin are correlated with particular functions and discrete steps of the mode of action of the

protein. Thus, a rational scheme for determining the regions of a delta-endotoxin that would tolerate modification is provided. Such a scheme eliminates the need to make random substitutions.

For example, based on the regions of delta-endotoxins that are conserved among protein family members, the skilled artisan could choose among possible modifications to produce polypeptides within the structural parameters set forth in the claims and then test these modified variants to determine if they retain pesticidal activity. In light of the guidance provided in the specification and the state of the art with respect to delta-endotoxins, a skilled artisan could readily conclude which amino acids are essential for structure and function and could envisage similar sequences that are 90% identical to the nucleotide sequence of SEQ ID NO:1, 3, or 5, or a nucleotide sequence encoding SEQ ID NO:2, 4, or 6, and that retain pesticidal activity. As such, one of skill in the art could identify the pesticidal sequences encompassed by the present claims without undue experimentation.

The Examiner contends that the teachings of de Maagd *et al.* (1999) *Appl. Environ. Microbiol.* 65:4369-4374, Tounsi *et al.* (2003) *J. Appl. Microbiol.* 95:23-28 and Angsuthanasombat *et al.* (2001) *J. Biochem. Mol. Biol.* 34:402-407 support the assertion that amino acid substitutions in delta-endotoxin proteins are unpredictable. The Examiner further suggests that none of the specificity-altering mutations of these references falls within the conserved regions described in the specification. The Applicants respectfully disagree.

de Maagd *et al.* teach that the insertion of several groups of amino acids (blocks A-F) within Domain III of Cry1E with the corresponding amino acids of Cry1C will alter the specificity and/or toxicity of Cry1E. At least 3 of these blocks (blocks A, B, and F) map to the conserved regions described on page 4 of the instant specification (provided in Appendix A of the amendment filed October 16, 2006). Blocks B and D were described by de Maagd *et al.* as being important for the specificity of these toxins toward *S. exigua* and *M. sexta*. With the exception of blocks C and F, each of the blocks of substituted amino acids contained at least 2 (and up to 8) non-conservative substitutions. Thus, each of the specificity-altering substitutions either occurs in a conserved region, or involves a non-conservative substitution.

Similarly, Tounsi *et al.* discuss the single amino acid difference between Cry1Ia1 and Cry1Ia2 (which is a non-conservative substitution of aspartic acid for tyrosine at position 233) as being critical to insecticidal specificity of these two toxins. Finally, while Angsuthanasombat *et al.* teach a critical amino acid residue at position 136 where even a conservative substitution could lead to loss of pesticidal activity, the majority of the loss-of-function substitutions were non-conservative in nature. The Applicants do not presume that every conceivable conservative substitution in a nonconserved region will produce a protein with the recited activity, rather that the methods for making and testing substitutions within 90% sequence identity to SEQ ID NO:2, 4, or 6 is routine in the art, and the level of experimentation is not undue.

In establishing non-enablement, the burden rests initially with the Examiner to substantiate the unpredictability of the art and that, given the unpredictability, the specification does not provide sufficient information to guide those of skill to make and use the claimed invention across the full scope of the claims. In view of the discussion above, the references cited by the Examiner fails to support the position that claims 1-11, 19, 22, and 23 are not enabled.

The Examiner further maintains that the specification does not enable the transformation of any plant with a nucleotide sequence with 95% identity to the nucleotide sequence of SEQ ID NO:1, 3, or 5, or a nucleotide sequence encoding SEQ ID NO:2, 4, or 6 because undue trial and error experimentation would be required to screen for nucleotide sequences encompassed by the claims and plants transformed therewith to identify those plants with pesticidal activity. As discussed above, the amount of experimentation required to identify a nucleotide sequence that has 90% sequence identity to SEQ ID NO:1, 3, or 5, or to a nucleotide sequence encoding SEQ ID NO:2, 4, or 6 is not undue. Given the guidance provided in the specification and the knowledge in the art, the claims directed to transformation of a plant with a delta-endotoxin sequence, or variant or fragment thereof, are fully enabled.

In light of the above arguments, the level of skill and knowledge in the art, and the guidance provided in the specification, Applicants respectfully submit that the specification is enabling for the full scope of claims 1-11, 19, 22 and 23. Thus, the rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn.

Written Description

Claims 1-11, 19, 22 and 23 were further rejected under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement. The rejection is respectfully traversed.

The Examiner asserts that the disclosure is insufficient to support claims that are drawn to a genus of nucleic acids having 95% sequence identity to SEQ ID NO:1, 3, or 5, or nucleic acids encoding polypeptides having 95% identity to SEQ ID NO:2, 4, or 6. Claims 1, 22 and 23 have been amended to recite that the isolated nucleic acid sequences of the invention, as well as the plants and plant cell comprising the nucleic acid sequences of the invention, encompass nucleic acid sequences that have at least 90% nucleotide sequence identity to SEQ ID NO:1, 3, or 5, or encode a protein having at least 90% amino acid sequence identity to SEQ ID NO:2, 4, or 6.

In order to satisfy the written description requirement of 35 U.S.C. § 112, the application must reasonably convey to one skilled in the art that the applicant was in possession of the claimed subject matter at the time the application was filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). Every species encompassed by the claimed invention, however, need not be disclosed in the specification to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. *Utter v. Hiraga*, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988). The Federal Circuit has made it clear that sufficient written description requires simply the knowledge and level of skill in the art to permit one of skill to immediately envision the product claimed from the disclosure. *Purdue Pharm L.P. v. Faulding In.*, 230 F.3d 1320 1323, 596 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("One skilled in the art must immediately discern the limitations at issue in the claims.").

Moreover, the "Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, ¶ 1, 'Written Description' Requirement" state that a genus may be described by "sufficient description of a representative number of species . . . or by disclosure of relevant, identifying characteristics , *i.e.* structure or other physical and/or chemical properties." *Id.* at 1106. This is in accordance with the standard for written description set forth in *Regents of the University of California v. Eli Lilly & Co*, 119 F.3d 1559 (Fed. Cir. 1997), where the court held that "[a] written description of an invention involving a chemical genus, like a description of a chemical

species, 'requires a precise definition, such as by structure, formula, or chemical name' of the claimed subject matter sufficient to distinguish it from other materials." 119 F.3d at 1568, citing *Fiers v. Revel* 984 F.2d 1164 (Fed. Cir. 1993). In *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.2d 926 (Fed. Cir. 2002), the Federal Circuit adopted the PTO standard for written description, stating:

> [U]nder the Guidelines, the written description requirement would be met . . . if the functional characteristics of [a genus of polypeptides] were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed. We are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement."

The claims of the present application meet the requirements for written description set forth by the Federal Circuit. The claims as amended recite that the nucleic acid have 90% sequence identity to the nucleotide sequence of SEQ ID NO:1, 3, or 5, or to a nucleotide sequence encoding SEQ ID NO:2, 4, or 6. Methods for determining percent identity between any two sequences are known in the art and are provided in the specification. See pages 9-13. As discussed above, nucleotide sequences for full-length AXMI-009 (SEQ ID NO:1), as well as variants and fragments (e.g., SEQ ID NO:3 and 5) are disclosed in the specification. Numerous delta-endotoxin sequences were also generally known in the art at the time the application was filed. Moreover, detailed information regarding the structure of delta-endotoxins and the reported functions associated with particular structures, regions, and motifs was also available in the prior art as well as discussed in detail on page 2, lines 21-29, Figure legend 1, and on page 12.

At the time of filing, it was known that delta-endotoxins generally comprise three domains, a seven-helix bundle that is involved in pore formation, a three-sheet domain that has been implicated in receptor recognition, and a beta-sandwich motif. See Li *et al.* (1991) *Nature* 305:815-821. Thus, the recitation of polypeptides having a particular percent identity to a delta-endotoxin provides very specific and defined structural parameters of the sequences that can be used in the invention. These structural limitations are sufficient to distinguish the nucleotide and

amino acid sequences of the invention from other nucleic acids and polypeptides and thus sufficiently define the genus of sequences useful in the practice of the present invention.

The Examiner maintains that the specification describes no relevant characteristics or motifs for the claimed nucleic acids other than identity to SEQ ID NO:1, 3, or 5, and that the level of skill and knowledge in the art at the time of filing is such that no other proteins within the scope of the claims were known. Applicants acknowledge that no other proteins within the scope of the claims were known; hence, the novelty of the invention. However, Applicants respectfully disagree with the assertion that no relevant characteristics or motifs were disclosed. As discussed above, domains associated with specific functions were known (Li *et al.*, *supra*), and conserved regions within each of these functional domains are described in the specification. Although the Examiner dismisses the relevance of these teachings since they describe a cry3Aa protein (pages 8- 9 of the August 15, 2006 Office Action), Li *et al.* state that the overall structure of this delta-endotoxin represents the general fold of the family of active delta-endotoxin proteins (see the abstract of Li *et al.*), and that the core of the cry3Aa molecule is built from the five sequence blocks that are highly conserved throughout the delta-endotoxin family (column 2, page 817 of Li *et al.*). These highly conserved sequence domains have been described in the instant specification as they relate to the delta-endotoxin of the invention.

The Examiner is also reminded that the description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. 66 Fed. Reg. 1099, 1106 (2000). Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. 66 Fed. Reg. 1099, 1106 (2000). Here, Applicants have provided nucleotide and amino acid sequences for exemplary pesticidal sequences and variants and fragments thereof encompassed by the claims. Moreover, numerous delta-endotoxin sequences were known and readily available in the art. Therefore, Applicants submit that in view of the present disclosure and the knowledge and level of skill in the art the skilled artisan would envision the claimed invention.

The description of a claimed genus can be by structure, formula, chemical name, or physical properties. *See Ex parte Maizel*, 27 USPQ2d 1662, 1669 (B.P.A.I. 1992), *citing Amgen v. Chugai*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). A genus of polypeptides may therefore be described by means of a recitation of a representative number of amino acid sequences that fall within the scope of the genus, *or* by means of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *See Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997); *see also* Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2000). The recitation of a predictable structure (i.e., an amino acid sequence having a specified percent identity or number of contiguous amino acid residues of a particular sequence) is sufficient to satisfy the written description requirement. Thus, the application provides the structural features that characterize sequences having at least 90% sequence identity to SEQ ID NO:1, 3, or 5, or to a nucleotide sequence encoding SEQ ID NO:2, 4, or 6 that retain pesticidal activity.

An Applicant may also rely upon functional characteristics in the description, provided there is a correlation between the function and structure of the sequences recited in the claims. *Id.*, citing *Lilly* at 1568. The present claims further recite functional characteristics that distinguish the sequences of the claimed genus. Specifically, the claims as amended recite that the sequences having at least 90% sequence identity to SEQ ID NO:1, 3, or 5, or to a nucleotide sequence encoding SEQ ID NO:2, 4, or 6 encode proteins which have pesticidal activity. The specification and the art provide standard assays that may be used to measure pesticidal activity. See, for example, page 8, lines 27-31. Furthermore, as noted above, Applicants have disclosed fragment sequences that retain pesticidal activity (e.g., SEQ ID NO:3 and 5, which encode fragments of SEQ ID NO:2). Accordingly, both the structural and functional properties that characterize the genus of sequences that can be used to practice the invention are specifically recited in the claims. The sequences that fall within the scope of the claims can readily be identified by the methods set forth in the specification.

In summary, the specification provides an adequate written description of the claimed invention. In particular, the specification provides: nucleotide and amino acid sequences for

pesticidal toxins, and variants and fragments thereof, that fall within the scope of the claims; guidance regarding sequence alterations that do not disrupt pesticidal activity of a toxin; guidance for determining percent identity; and methods for assaying the pesticidal activity of proteins. In view of the above remarks and claim amendments, Applicants submit that the relevant identifying structural and functional properties of the genus of sequences of the present invention would be clearly recognized by one of skill in the art. Consequently, Applicants were in possession of the invention at the time the application was filed, and the rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of written description should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

The rejection of claim 11 under 35 U.S.C. § 112, second paragraph has been maintained as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention.

Claim 11 has been amended to recite "a transgenic seed comprising the nucleic acid molecule of claim 1. Therefore, as amended, claim 11 now describes a transgenic seed that comprises the nucleic acid of claim 1. Accordingly, the rejection of claim 11 under 35 U.S.C. § 112, second paragraph should be withdrawn.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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